# Contribution of Voltage-Gated $Ca^{2+}$ Channels to Homosynaptic Long-Term Depression in the CA1 Region In Vitro

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**Christie, Brian R., Lalania K. Schexnayder, and Daniel Johnston.** Contribution of voltage-gated $Ca^{2+}$ channels to homosynaptic long-term depression in the CA1 region in vitro. *J. Neurophysiol.* 77: 1651–1655, 1997. Homosynaptic long-term depression (LTD) of synaptic efficacy was induced in field excitatory postsynaptic potentials by administration of 900 pulses at either 1 or 3 Hz in 2- to 3-wk-old Sprague-Dawley rats. The stimulation was administered via a bipolar stimulating electrode placed immediately adjacent to the recording electrode in the stratum radiatum region of the hippocampal CA1 subfield. Equivalent LTD induction occurred whether the slices were maintained at room temperature or at 32°C. Lowering bath $Ca^{2+}$ to 0 mM, or increasing it to 4 mM, prevented the induction of the depression. The NMDA receptor antagonist D,L-2-amino-5-phosphonovaleric acid (50 $\mu$M) reversibly blocked the induction of homosynaptic LTD. In addition, the L-type voltage-gated calcium channel (VGCC) antagonist nimodipine (10 $\mu$M) and the R- and T-type VGCC antagonist $NiCl_2$ (25 $\mu$M) also prevented homosynaptic LTD induction. These results indicate that in addition to *N*-methyl-D-aspartate receptor activity, $Ca^{2+}$ influx via VGCCs can play an important role in the induction and expression of LTD induced by low-frequency stimulation in the hippocampal formation.

## INTRODUCTION

The *N*-methyl-D-aspartate (NMDA) receptor is thought to play a critical role in the genesis of homosynaptic long-term depression (LTD) of synaptic efficacy in the CA1 region of the hippocampal formation (Bliss and Collingridge 1993; Christie et al. 1995). In addition, an increase in postsynaptic $Ca^{2+}$ is also believed to play a critical role in the genesis of LTD in this area (Bolshakov and Siegelbaum 1994; Mulkey and Malenka 1992). What remains controversial is whether the rise in postsynaptic $Ca^{2+}$ that is involved in the genesis of LTD is due to the activation of NMDA receptors (Dudek and Bear 1992; Selig et al. 1995), the activation of voltage-gated calcium channels (VGCCs; Bolshakov and Siegelbaum 1994), or some combination of both.

Imaging studies of single CA1 pyramidal neurons indicate that the rise in postsynaptic $Ca^{2+}$ following synaptic stimulation is primarily due to $Ca^{2+}$ entry via VGCCs (Jaffe et al. 1992; Miyakawa et al. 1992; Regehr et al. 1989). Fluorescence imaging studies have also indicated that there are several types of VGCCs that are located in CA1 pyramidal cell somata and throughout the dendrites (Christie et al. 1995; Regehr and Tank 1992). Although the overall density of $Ca^{2+}$ channels does not appear to change in more distal dendritic regions (Magee and Johnston 1995), the relative contribution of the different channel subtypes to postsynaptic $Ca^{2+}$ influx differs between somatic and dendritic regions (Christie et al. 1995; Magee and Johnston 1995). Calcium entry in the proximal dendrites of CA1 neurons is mainly due to the activity of L-type VGCCs (Christie et al. 1995; Jaffe et al. 1992). As one progresses further out into the apical dendrites (>150 $\mu$m), the contribution of R- and T-type VGCCs increases (Christie et al. 1995; Magee and Johnston 1995). Unlike high-threshold VGCCs, these low-threshold T channels can be activated by synaptically activated excitatory postsynaptic potentials (EPSPs) (Magee et al. 1995), indicating that they can provide a source of $Ca^{2+}$ in the absence of back-propagating action potentials. The aims of the present experiments were to examine further the sensitivity of homosynaptic LTD to different VGCC blockers. Portions of this work have been presented previously in abstract form (Schexnayder et al. 1995).

## METHODS

Hippocampal slices were prepared from young Sprague-Dawley rats (14–28 days) with the use of procedures we have described previously (Christie et al. 1995). Briefly, rats were decapitated and the brain was rapidly dissected in cold artificial cerebrospinal fluid (ACSF) composed of (in mM) 124 NaCl, 26 $NaHCO_3$, 10 dextrose, 2.5 KCl, 2.5 $CaCl_2$, 1.5 $MgCl_2$, and 1.25 $NaH_2PO_4$, superfused with 95% $O_2$-5% $CO_2$. with the use of a vibratome, serial slices (400 $\mu$m) were taken from the dorsal hippocampus and placed in an oxygenated holding chamber. Slices were incubated at 35°C for ≥20 min and then stored at room temperature 23°C for the remainder of the experiment (<6 h). Electrophysiological recordings were carried out at either 23 or 32°C with the use of conventional field recording in a submerged chamber. Field EPSPs (f-EPSPs) were recorded from the stratum radiatum in the CA1 region with the use of glass electrodes filled with 1 M NaCl. Constant current stimuli were delivered with a bipolar tungsten wire electrode placed on the stratum radiatum immediately adjacent to the recording electrode. To monitor the f-EPSP slope, individual stimuli were administered every 15 s. To induce LTD, low-frequency stimulation (LFS; 900 pulses) was administered at either 1 or 3 Hz with the use of the same intensity stimuli used to monitor f-EPSPs. D,L-2-amino-5-phosphonovaleric acid (D,L-APV; 50 $\mu$M; RBI) and $NiCl_2$ (25 $\mu$M; Sigma) were prepared daily from 5 mM stock solutions. Nimodipine (10 $\mu$M; RBI) was prepared daily in ethanol, and all recordings were performed in a darkened room. All data presented in the text are means ± SE of 20 responses recorded over a 5-min period (25–30 min postconditioning) unless otherwise stated. Data points in figures represent averages of 20 responses recorded over 5-min periods. Statistical analysis was performed with the use of unpaired *t*-tests, with significance levels set at $P = 0.05$.

## RESULTS

Recently, inhibitors of nitric oxide have been shown to block long-term potentiation (LTP) in the CA1 region, but

 

only when recordings are made at room temperature, and not when slices are maintained at higher temperatures where LTP of a greater magnitude can be induced with the same stimulus protocol (Williams et al. 1993). To test the possibility that low-frequency-induced homosynaptic LTD might also exhibit a temperature dependence, trains of conditioning stimuli were administered at either room temperature (23°C) or at 32–35°C, and f-EPSPs were recorded. A significant depression of synaptic efficacy was observed at room temperature, for both the 1-Hz (−20.17 ± 7.5%, mean ± SE, $n = 6$, $P < 0.05$; Fig. 1*A*) and 3-Hz (−22.17 ± 2.2, $n = 5$, $P < 0.05$; Fig. 1*B*) stimuli. In contrast to what has been observed for LTP in this region, increasing the bath temperature to 32–35°C did not produce significantly greater LTD with either frequency (1 Hz: −20.72 ± 7.5, $n = 6$; 3 Hz: −25.5 ± 10.2, $n = 5$; Fig. 1, *A* and *B*). This indicates that homosynaptic LTD induction is not as temperature sensitive as LTP, making it ideal to examine in behavioral situations where brain temperature can vary markedly (Moser et al. 1993). In addition to the lack of temperature dependence, the 1- or 3-Hz stimuli produced nearly equivalent LTD of the f-EPSP. The remaining experiments were all conducted at 32°C. To ensure that the LTD under investigation was similar to that observed by others (Bolshakov and Siegelbaum 1994; Dudek and Bear 1992; Mulkey and Malenka 1992; Selig et al. 1995), 50 μM D,L-APV was added to the bath in an attempt to block the induction of the LTD. As shown in Fig. 1*C*, D,L-APV completely blocked the induction of homosynaptic LTD with both the 1- and 3-Hz stimulation (1 Hz: 5.0 ± 13.2, $n = 6$; 3 Hz: 27.5 ± 9.8, $n = 8$; Fig. 1*C*), although LTD could still be induced after washout of the drug (1 Hz: −36.8 ± 12.4; 3 Hz: −18.0 ± 6.5; Fig. 1*C*).

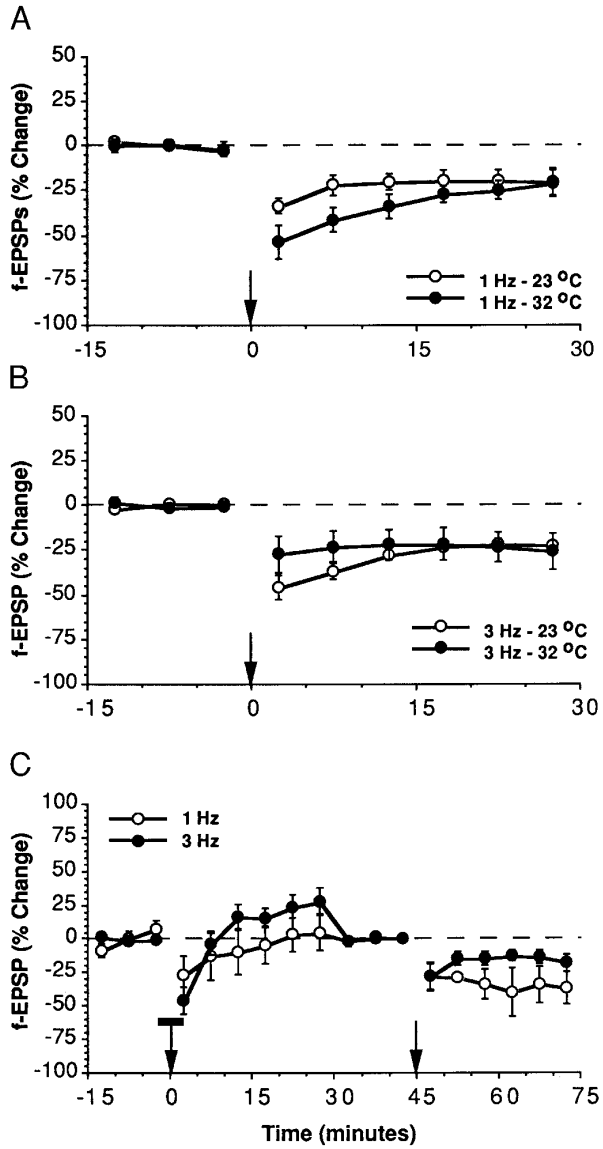


FIG. 1. Homosynaptic long-term depression (LTD) induction is not temperature dependent. *A*: application of 900 pulses at 1 Hz produced a significant depression of evoked field responses at both 23 and 32°C. No difference in the magnitude of LTD was evident at 30 min postconditioning. *B*: 3-Hz stimuli also produced significant and equivalent LTD at 23 and 32°C. *C*: application of low-frequency stimulation (LFS) in the presence of D,L-2-amino-5-phosphonovaleric acid (D,L-APV) (solid bar) does not result in the induction of homosynaptic LTD with either the 1- or 3-Hz stimuli. When the same stimuli are applied in normal artificial cerebrospinal fluid (ACSF), LTD is produced. Arrows: time point at which conditioning stimulation was applied.

To examine the involvement of $Ca^{2+}$, we initially tested field responses in slices perfused with ACSF containing either low ($Ca^{2+}$ free), normal (2.5 mM), or high (4 mM) $Ca^{2+}$. For the low-$Ca^{2+}$ condition, slices were first tested in normal ACSF to acquire stable baseline recordings. The ACSF was then switched to one that contained 0 mM $Ca^{2+}$, and perfused for 5 min to reduce the bath calcium level significantly (Christie et al. 1995). During this period responses diminished to 0–5% of their initial size, and then 3-Hz stimulation was applied while the calcium-free perfusion continued for an additional 5 min. After the application of the 3 Hz stimuli, the solution was switched back to one containing normal $Ca^{2+}$. Slices bathed in a $Ca^{2+}$-free solution immediately before and during the low-frequency trains did not exhibit homosynaptic LTD, as measured 30 min postconditioning (9.04 ± 5.0%, $n = 4$, $P > 0.05$; Fig. 2*A*). Slices that were then readministered the LFS in normal $Ca^{2+}$ exhibited LTD of the field response similar to that shown previously (−28.8 ± 10.1%, $n = 4$; see also Fig. 1*B*). In the elevated $Ca^{2+}$ condition, recordings were made from slices continuously bathed in ACSF containing 4 mM $Ca^{2+}$, after the acquisition of baseline responses in normal ACSF. In these animals, even though the size of the fiber volley remained unchanged, the amplitude and the slope of the f-EPSP increased in the presence of the 4 mM $Ca^{2+}$. In this condition the application of the 3-Hz stimuli also failed to produce homosynaptic LTD, and in fact produced a slight potentiation (16.7 ± 12.0%, $n = 7$; Fig. 2*B*). When the external $Ca^{2+}$ was then lowered back to 2.5 mM, it was possible to depress the evoked responses from their elevated levels to a point below the original baseline level (−10 ± 18.8%, $n = 7$).

Patch-clamp and fluorescence imaging data indicate that the L-, R-, and T-type VGCCs are the primary VGCCs active in the apical dendrites of CA1 pyramidal cells (Christie et al. 1995; Magee and Johnston 1995; Magee et al. 1995). Previously it has been reported that homosynaptic LTD is both sensitive and insensitive to L-type VGCC antagonists (Bolshakov and Siegelbaum 1994; Selig et al. 1995). LTD

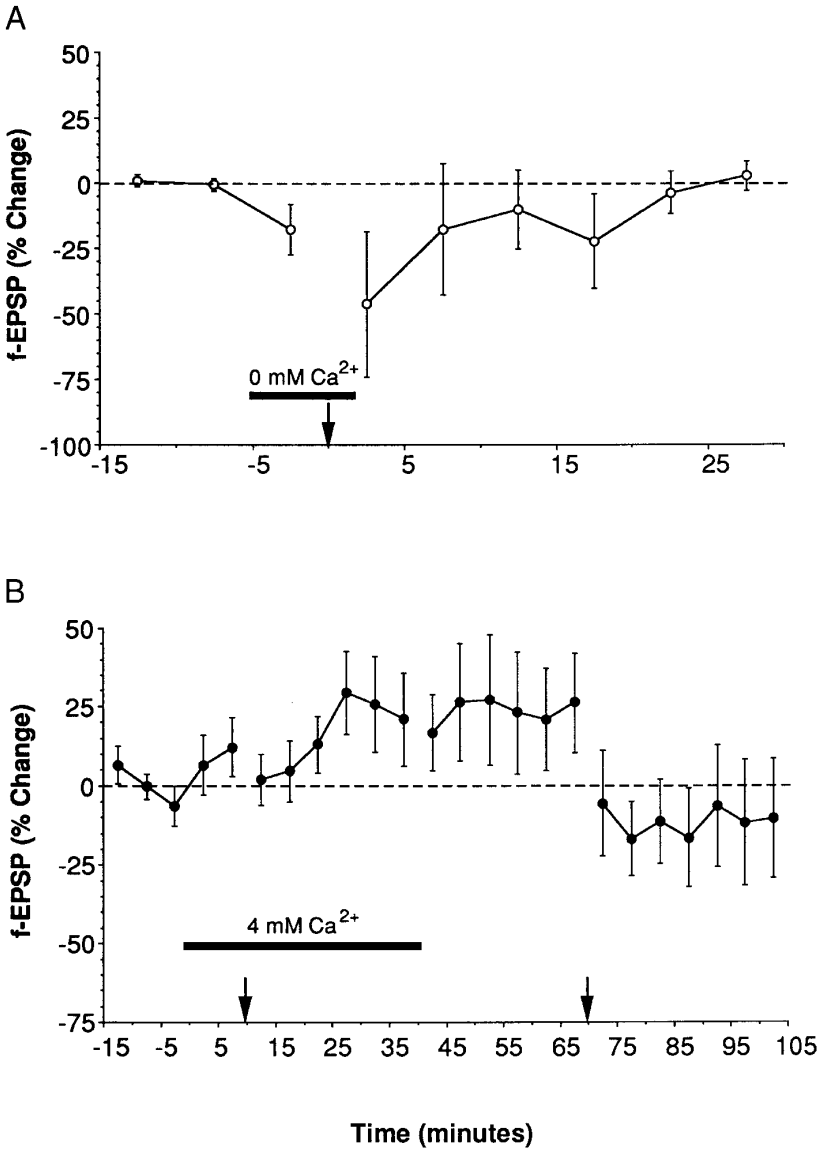


FIG. 2. External $Ca^{2+}$ levels influence the expression of homosynaptic LTD. *A*: field responses recorded before and after perfusion of the slice with a $Ca^{2+}$-free solution. LFS (3 Hz) was administered in the presence of the 0 mM calcium bathing medium. Responses recorded after the restoration of normal external $Ca^{2+}$ levels fail to exhibit LTD. *B*: increasing extracellular $Ca^{2+}$ to 4 mM (solid bar) disrupts the induction of LTD and a slight potentiation is produced by the LFS. When the extracellular medium is switched back to one containing 2.5 mM $Ca^{2+}$, application of the LFS depresses evoked responses. Arrows: time point at which conditioning stimulation was applied.

was blocked by the L-type antagonist nitrendipine (Bolshakov and Siegelbaum 1994), whereas no effect was observed when nifedipine was used to block L-type channels in young animals (Selig et al. 1995). For our experiments we chose to use nimodipine, a potent and relatively nonphotolabile blocker of L-type VGCCs that has been used to block heterosynaptic LTD both in vitro (Wickens and Abraham 1991) and in vivo (Christie and Abraham 1994). Because nimodipine may cause a small increase in evoked EPSPs when bath applied, this compound was included in the bath continuously for these experiments (O'Regan et al. 1991). Nimodipine (10 $\mu$M) prevented the induction of homosynaptic LTD with both the 1- and 3-Hz stimulation (1 Hz: 0.8 $\pm$ 9.4, $n = 4$; 3 Hz: 12.3 $\pm$ 8.4, $n = 4$; Fig. 3). Owing to the lack of a specific blocker for the R- and T-type VGCCs, we used $NiCl_2$, which acts on both of these channels (Avery and Johnston 1996; Magee and Johnston 1995). All experiments were performed with the use of 25 $\mu$M $NiCl_2$, a concentration that we (Schexnayder et al. 1995) and others (Ito et al. 1995) have found does not alter synaptic transmission. When 25 $\mu$M $NiCl_2$ was applied to the slice during the induction procedure, LTD induction was prevented with both the 1- and 3-Hz stimulation protocols (1 Hz: 2.5 $\pm$ 11.2, $n = 6$; 3 Hz: 12.6 $\pm$ 12.1, $n = 5$; Fig. 3*B*). Attempts to induce LTD 30–45 min after $NiCl_2$ washout invariably failed, despite the fact that f-EPSPs appeared unaffected by the drug.

## DISCUSSION

The present study indicates that bath temperature does not dramatically influence the degree of depression observed after the application of LFS. Equivalent LTD was produced at both 23 and 32°C. In contrast, the extracellular bath concentration of $Ca^{2+}$ had profound effects on LTD induction. When a $Ca^{2+}$-free solution was washed in before the application of the induction protocol, synaptic transmission was reduced markedly, and no EPSPs were recorded during the LFS stimulation. Although it is unclear whether the lack of LTD was due to a failure to either evoke transmitter release or induce a postsynaptic $Ca^{2+}$ influx, LFS-induced homosyn-

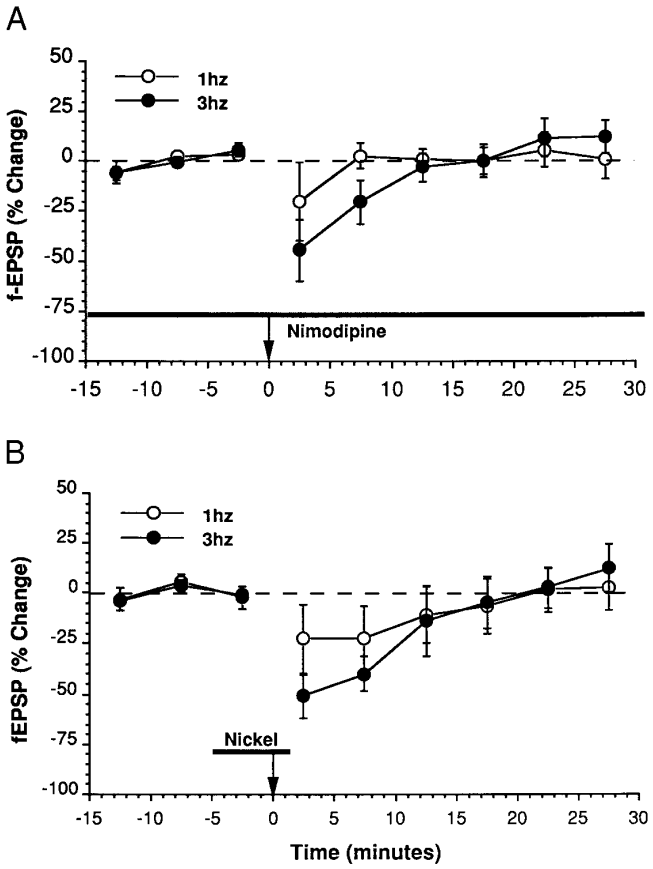


FIG. 3. Blockade of voltage-gated calcium channels (VGCCs) prevents LTD induction. *A*: L-type VGCC antagonist nimodipine (10 $\mu$M) prevented the induction of LTD with both the 1- and 3-Hz stimuli. *B*: addition of the R- and T-channel antagonist $NiCl_2$ (25 $\mu$M) to the recording medium during the application of the LFS also prevents the induction of homosynaptic LTD. Arrows: time point at which conditioning stimulation was applied.

aptic LTD does not appear to be the result of some stimulation-induced pathology, because responses fully recovered after a return to normal medium. The reason for the lack of LTD in the high-$Ca^{2+}$ medium is also hard to interpret, because this may reflect changes in the amount of transmitter being released, an increase in postsynaptic $Ca^{2+}$, or an alterations in membrane protein functioning due to changes in the screening charge. Again, prolonged LFS did not generate an LTD in this situation, indicating that LTD is not dependent on stimulation alone. Furthermore, responses were able to be depressed when these slices were administered the LFS in normal medium.

A main finding of the present study is that $Ca^{2+}$ influx via at least two subtypes of VGCCs appears to play an important role in the induction of homosynaptic LTD in the CA1 region in vitro. The fact that the L-type VGCC antagonist nimodipine prevented the induction of homosynaptic LTD also supports the findings of Bolshakov and Siegelbaum (1994), who prevented homosynaptic LTD induction in slices obtained from very young animals with the L-type VGCC antagonist nitrendipine. It remains unclear why a third L-type antagonist, nifedipine, has been unsuccessful in preventing LTD induction in animals of similar age (Mulkey and Malenka 1992; Selig et al. 1995). This may reflect a difference in the experimental methodology or a difference in the site of action of these antagonists. In addition to the contribution of L channels to homosynaptic LTD, it also appears that either or both the R and the T subtypes of VGCC contribute to the genesis of homosynaptic LTD. These channels are richly distributed in the apical dendrites of CA1 pyramidal neurons (Christie et al. 1995; Magee and Johnston 1995), where they are able to provide a source of $Ca^{2+}$ in response to both weak and strong synaptic stimulation (Magee et al. 1995). Recent evidence from our laboratory indicates that stimuli subthreshold for the generation of action potentials are insufficient to generate LTD in individual neurons (Christie et al. 1995). This would indicate that it is more likely that R- rather than T-type VGCCs are active in homosynaptic LTD. Fluorescence imaging studies indicate that $Ca^{2+}$ influx via high-threshold L- and R-type VGCCs occurs only when somatic action potentials are generated (Christie et al. 1995; Magee et al. 1995), suggesting a role for such activity in LTD. It seems possible that the involvement of the NMDA receptor might be to prolong the period of postsynaptic depolarization so that VGCCs are more likely to be activated, and, under the present stimulus protocol, LTD is induced. Hell et al. (1996) have in fact shown that NMDA receptor activation in CA1 cells may persistently increase $Ca^{2+}$-influx through at least L-type channels after intense synaptic activity (see also Chetkovich et al. 1991). It is interesting that homosynaptic LTD, like LTP in this region, is susceptible to manipulations that alter the levels of postsynaptic $Ca^{2+}$ in the dendrites and somata of CA1 pyramidal cells. Both LTP and LTD have been prevented in the CA1 region by antagonists of NMDA receptors (Collingridge et al. 1983; Dudek and Bear 1992; present study), L-type VGCC antagonists (Bolshakov and Siegelbaum 1994; Grover and Teyler 1990; present study) and now by the R- and T-type VGCC antagonist $NiCl_2$ (Ito et al. 1995; present study). What remains unclear, however, is the mechanism by which these channels exert their actions in LTD genesis. Clearly a rise in postsynaptic $Ca^{2+}$, without concurrent postsynaptic channel activation, is insufficient to reliably generate LTD (Neveu and Zucker 1996). It is possible that the key factor for LTD genesis remains some level of postsynaptic $Ca^{2+}$ (Lisman 1994), and that any manipulation that substantially reduces postsynaptic $Ca^{2+}$ entry prevents LTD, but it also remains plausible that the manner in which this $Ca^{2+}$ reaches the intracellular space is also highly critical.

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